

CPY
PREPUBLICATION COPY

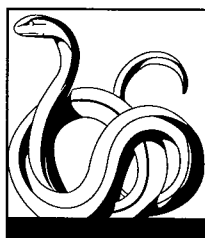
Executive Summary

1993

VETERANS AND AGENT ORANGE

Health Effects of Herbicides Used in Vietnam

DISTRIBUTION STATEMENT A
Approved for Public Release
Distribution Unlimited



INSTITUTE OF MEDICINE

20040308 364

**EXECUTIVE SUMMARY
PREPUBLICATION COPY**

**Veterans and Agent Orange:
Health Effects of Herbicides Used in Vietnam**

Committee to Review the Health Effects in
Vietnam Veterans of Exposure to Herbicides

Division of Health Promotion and
Disease Prevention

INSTITUTE OF MEDICINE



NATIONAL ACADEMY PRESS
Washington, D.C. 1993

National Academy Press ■ 2101 Constitution Avenue, N.W. ■ Washington, D.C. 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

Support for this study was provided by the Department of Veterans Affairs (contract no. V101(93)P-1331).

This Executive Summary is available in limited quantities from the Institute of Medicine, Division of Health Promotion and Disease Prevention, 2101 Constitution Avenue, N.W., Washington, DC 20418.

The complete volume of *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, from which this Executive Summary is extracted, is available for sale from the National Academy Press, 2101 Constitution Avenue, N.W., Box 285, Washington, DC, 20055. Call 800-624-6242 or 202-334-3938 (in the Washington Metropolitan Area).

Copyright 1993 by the National Academy of Sciences. All rights reserved.

Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logo-type by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliches Museum in Berlin.

**COMMITTEE TO REVIEW THE HEALTH EFFECTS IN
VIETNAM VETERANS OF EXPOSURE TO HERBICIDES**

- HAROLD FALLON (*Chairman*), Dean, School of Medicine, University of Alabama, Birmingham, Alabama
- DAVID TOLLERUD (*Vice-Chairman*), Director, Occupational and Environmental Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania
- NORMAN BRESLOW (*Liaison to the IOM Board on Health Promotion and Disease Prevention*), Professor, Department of Biostatistics, University of Washington, Seattle, Washington
- JESSE BERLIN, Research Assistant Professor of Biostatistics in Medicine, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
- KAREN BOLLA, Assistant Professor, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland
- GRAHAM COLDITZ, Associate Professor of Medicine, Harvard Medical School, Boston Massachusetts
- CHRISTOPHER GOETZ, Director, Department of Neurologic Sciences, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois
- NORBERT KAMINSKI, Assistant Professor, Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond, Virginia
- DAVID KRIEBEL, Associate Professor, Department of Work Environment, University of Massachusetts, Lowell, Massachusetts
- N. KARLE MOTTET, Professor, Department of Pathology and Environmental Health, University of Washington School of Medicine, Seattle, Washington
- ALFRED NEUGUT, Associate Professor, Department of Medicine and School of Public Health, Columbia University College of Physicians and Surgeons, New York, New York
- WILLIAM NICHOLSON, Professor, Mount Sinai School of Medicine, New York, New York
- ANDREW OLSHAN, Assistant Professor, Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, North Carolina
- KATHLEEN RODGERS, Associate Professor, Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles, California
- NANCY SPRINCE, Associate Professor, Department of Preventive Medicine, University of Iowa, Iowa City, Iowa
- CLIFFORD WEISEL, Assistant Professor, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey

Project Staff

MICHAEL STOTO, Project Director and Director, Division of Health Promotion and
Disease Prevention
SUSAN ROGERS, Program Officer
DIANE MUNDT, Program Officer
CYNTHIA ABEL, Research Associate
CATHARYN LIVERMAN, Research Associate
CATHERINE WESNER, Project Assistant
ZOE SCHNEIDER, Project Assistant

Staff Consultants

GAIL CHARNLEY, Consultant, Board on Environmental Studies and Toxicology, National
Research Council
JANE DURCH, Program Officer, Institute of Medicine
THOMAS BURROUGHS, Contract Science Writer
FLORENCE POILLON, Contract Editor
ANDREA POSNER, Contract Copy Editor
JANA KATZ, Student Intern

Institute of Medicine

KENNETH I. SHINE, President
ENRIQUETA C. BOND, Executive Officer
MICHAEL EDINGTON, Managing Editor

Foreword

In response to decades of concern surrounding the possible long-term health consequences of exposures to herbicides and the contaminant dioxin, Congress directed the Secretary of Veterans Affairs, in Public Law 102-4 signed on February 6, 1991, to request the National Academy of Sciences (NAS) to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used during the Vietnam conflict. This report from the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides is hereby submitted in compliance with Public Law 102-4.

Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam reviews and evaluates the available scientific evidence regarding the association between exposure to dioxin or other chemical compounds in herbicides used in Vietnam and a wide range of health effects, and provides the committee's best assessment of this body of knowledge for the Secretary of Veterans Affairs to consider as the Department of Veterans Affairs exercises its responsibilities to Vietnam veterans. The report also describes areas in which the available scientific data are insufficient to determine whether an association exists and provides the committee's recommendations for areas in which future research is likely to be most productive.

That Congress would ask the NAS--a nongovernmental organization--to conduct this study reflects a time-honored tradition. Created by an act of Congress and signed into law in 1863 by President Abraham Lincoln, the NAS is dedicated to the furtherance of science and technology and to their use for the promotion of general public welfare. A private, nonprofit society of distinguished scholars engaged in scientific and engineering research, the NAS has a mandate to advise the federal government on scientific and technical issues of pressing importance. Its members, drawn from universities and the private sector, are elected by their peers on the basis of exemplary professional achievement. Members, along with other leading experts, voluntarily participate in National Research Council and IOM studies and serve without compensation.

The IOM was chartered by the NAS in 1970 to serve as an adviser to the federal government on issues that affect the public's health, as well as to act independently in identifying important issues of medical care, research, and education. The IOM brings to this mission more than two decades of experience in conducting independent analyses of pressing health problems that involve federal policy decisions.

As described in more detail in Chapter 2 of this report, the NAS has a history of

involvement with the Agent Orange issue. A major study in 1974 focused primarily on the possible ecological consequences of herbicides used in Vietnam, but an individually authored component of that report published eight years later reviewed its possible reproductive effects among the Vietnamese. In the early 1980s, two committees reviewed protocols for large, epidemiologic studies of the health effects in veterans. Between 1986 and 1990, an IOM committee reviewed protocols and the analytical methods of a series of epidemiologic studies of Vietnam veterans carried out by the Centers for Disease Control, though it did not contribute to the final conclusions reached in those studies. Thus, while the NAS and the IOM have been aware of the controversy surrounding the military use of Agent Orange and other herbicides in Vietnam, these past activities are quite different from the current study, of which the primary purpose is to determine whether there are health effects related to exposure to herbicides.

The 16-members of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides represent a wide range of expertise including occupational and environmental medicine, toxicology, epidemiology, pathology, clinical oncology, psychology, neurology, and biostatistics. The committee was chaired by Harold Fallon, M.D., Dean of the Medical School at the University of Alabama, Birmingham, and a member of the IOM. David Tollerud, M.D., M.P.H., Director of Occupational and Environmental Medicine at the University of Pittsburgh, served as vice-chair. Committee member Norman Breslow, Professor of the Department of Biostatistics of the University of Washington and also a member of the IOM, served as a liaison to the IOM Board on Health Promotion and Disease Prevention, which was responsible for overseeing this study. Biographical sketches of the other committee members and the professional staff appear in Appendix D.

All committee members were selected because they are leading authorities in their scientific fields, are well-respected by their colleagues and peers, have no conflicts of interest with regard to the matters under study, and, indeed, have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or dioxin exposure. The committee thus has provided a fresh analysis of this issue--which is both scientifically complex and emotionally charged--and this report reflects the committee's thorough and unbiased scientific judgments. As with all reports from the IOM, the committee's work was reviewed by an independent panel of distinguished experts.

Kenneth I. Shine
President, Institute of Medicine

Preface

The use of Agent Orange and other herbicides in Vietnam has stimulated concern and controversy ever since the U.S. began the military herbicide program in 1962. Questions regarding the effects of herbicides on health and the environment have persisted over several decades. Many veterans, who served their country in Vietnam at great personal sacrifice and hardship, face continuing uncertainty about whether a myriad of diseases and health effects are associated with exposure to the herbicides used in Vietnam. Some of these veterans and their families feel that their pain and suffering have been ignored and that these questions have not been adequately addressed.

In response to the concerns voiced by Vietnam veterans and their families, Congress called upon the National Academy of Sciences (NAS) to review the scientific evidence on the possible health effects of exposure to herbicides. The creation of the NAS Institute of Medicine's committee underscores the critical importance of approaching these questions from a scientific standpoint, yet the committee realized from the beginning that it could not conduct a credible scientific review without a full understanding of the experiences and perspectives of veterans. Thus, to supplement its standard scientific process, the committee opened several of its meetings to the public to allow veterans and other interested individuals to voice their concerns and opinions, to provide personal information about individual exposure to herbicides and associated health effects, and to educate the committee on recent research results and studies still under way. This information provided a meaningful backdrop for the numerous scientific articles that the committee reviewed and evaluated. The committee appreciates the efforts of everyone who presented information to it and acknowledges this valuable addition to the study process.

As the study progressed, two separate but interdependent themes became evident to the committee. First, this report is a scientific investigation of the potential health effects of exposure to the herbicides that were used in Vietnam and to dioxin (2,3,7,8-tetrachlorodibenzo-*para*-dioxin; TCDD), an unintentional contaminant of some of those herbicides. This theme is discussed first in Chapter 2, which provides a context for the investigation by relating the history of national concern about TCDD and herbicides and of efforts to address this concern. Chapter 4 reviews the toxicological data (based on laboratory studies and animal investigations) on these chemicals, with a focus on the TCDD contaminant because this area has been the object of more substantial scientific research. Most of the committee's work, however, focused on the review of epidemiologic studies. Chapters 8 through 11 analyze and present the committee's conclusions regarding the relationship between herbicide/TCDD exposure and 44 specific diseases and disorders. These diseases and disorders include different forms of cancer,

reproductive and developmental effects, neurobehavioral disorders, and other health effects, including chloracne and porphyria cutanea tarda. In order to understand the committee's approach to these reviews, Chapter 5 lays out the general methodological considerations that the committee used in evaluating this evidence, and Chapter 6 addresses the question of how to assess the nature of exposure to the substances in question, a critical element in evaluating the epidemiologic studies that were reviewed. Many of these studies addressed the health effects of people who were occupationally or environmentally exposed to TCDD or the herbicides in question, and many of the studies investigated more than one health outcome. Rather than summarize the methods of these studies each time they are considered, the committee's review and summary of the health effects are preceded by a complete and thorough methodologic description of all the studies under review--organized by the nature of the population exposed and by study methods--in Chapter 7.

The second theme in this report relates to the use of herbicides in Vietnam, the effects of exposure on Vietnam veterans, and the direction of future research efforts toward learning more than is currently known about these issues. The discussion of this theme also begins in Chapter 2, but the history of military operations in Vietnam, with a special focus on the herbicide program, is described in detail in Chapter 3. In addition to addressing exposure assessment in general, Chapter 6 discusses the methods that have been used to assess exposure to herbicides in studies of Vietnam veterans and summarizes what is currently known about the nature and extent of that exposure. Chapter 6 also proposes a new method of historical exposure reconstruction in studies of Vietnam veterans, a topic that is the focus for the committee's research recommendations in Chapter 12. In addition, Chapter 12 comments on existing studies of Vietnam veterans and makes recommendations about four specific programs mandated in Public Law 102-4.

CONDUCT OF THE STUDY

The committee worked on several fronts in conducting this study, always with the goal of seeking the most accurate information and advice from the widest possible range of knowledgeable sources. Consistent with procedures of the Institute of Medicine (IOM), the committee met in a series of closed sessions and working group meetings in which members could freely examine, characterize, and weigh the strengths and limitations of the available evidence. Given the nature of the controversy surrounding this issue, the committee deemed it vital to convene open meetings as well. Three public meetings were held during the course of the study, which provided timely forums for veterans and veterans service organizations, researchers, policymakers, and other interested parties to present their concerns, review their research, and exchange information directly with the committee members.

The first open meeting was held in September 1992. To solicit broad participation, the IOM committee sent announcements to nearly 1,000 persons known to have an interest in this issue. Names were gathered from veterans service organizations, scientific organizations, labor unions, environmental groups, government agencies, and numerous other sources, and news of

the meeting was circulated to approximately 1,500 media outlets nationwide. During this day-long public meeting, 25 persons made oral presentations. Because some individuals were unable to attend the public meeting, written statements were given equal weight to oral presentations; by April 15, 1993, 28 additional individuals had submitted written statements. Besides these statements, the committee received specially prepared analyses from several groups. All of this material was carefully considered by the committee over the course of the study. The oral presentations and written statements submitted to the committee are described in detail in Appendix B.

The second public meeting, a "Scientific Workshop on Exposure Assessment," took place in December 1992. The committee assembled 17 experts in various scientific fields--drawn from universities, veterans service organizations, federal agencies, and health groups--to discuss how exposure to Agent Orange, other herbicides, and TCDD is assessed in epidemiologic studies. Participants discussed records-based methods, as well as more recent biomedical research in which current dioxin levels are measured in the blood and tissue of individuals to estimate previous levels of exposure to TCDD (see Appendix B).

A third public meeting, held in February 1993, focused on the "Vietnam Experience." The committee heard from veterans who had served in the U.S. Marines, Navy, Army, and Air Force. Some of these individuals experienced extensive combat, frequently in areas sprayed with herbicides. Others had been directly involved in spraying herbicides from aircraft or "brown water" river patrol boats. The committee also heard from the Vietnam Veterans of America on the wartime experiences of women, thousands of whom served in Vietnam, primarily as military nurses.

In addition to its formal meetings, the committee actively and continuously sought information from, and explained its mission to, a broad array of individuals and organizations with interest or expertise in assessing the effects of exposure to herbicides. These interactions included frequent meetings with representatives of veterans service organizations, congressional committees, federal agencies, and scientific organizations. The committee heard from the public through several hundred telephone calls and letters, each of which received a response from the IOM staff.

The committee also benefited from the expert advice and reviews of consultants in toxicology, environmental health, neurotoxicology, autoimmune disorders, reproductive effects, and dermatological disorders, including porphyria cutanea tarda. A list of the background papers, their authors, and the experts consulted appears in Appendix B.

During the course of the committee's work, the Environmental Protection Agency (EPA) has been in the process of carrying out an open scientific reassessment of the health risks of dioxin to guide its regulatory policy. The committee has benefited from this effort by being able to read and consider draft scientific reports prepared for the EPA by independent scientists as part of this process, and by IOM committee members' and staff's attendance at the EPA's public meetings. However, the congressional charge to the IOM committee is substantially different than the EPA's review in at least two important ways: (1) the EPA is concerned only with dioxin, whereas the IOM is concerned with all of the herbicides used in Vietnam, and (2)

because of its regulatory focus, the EPA is more concerned with defining a dose-response relationship than the IOM committee felt was either necessary or feasible for Vietnam veterans.

The value of this continued, open, and wide-ranging dialogue between the IOM committee and the scientific community, veterans, policymakers, and citizens proved itself many times over and ultimately contributed to a more comprehensive report.

Most of the committee's work involved reviewing the scientific literature bearing on the association between herbicides or dioxin and various health outcomes. The committee or its staff read approximately 6,420 abstracts of scientific or medical articles which were then entered into a computerized bibliographic data base. From these, approximately 230 epidemiologic studies were chosen for detailed review and analysis. These included studies of people exposed to the herbicides in question in occupational and environmental settings, as well as studies of Vietnam veterans. The committee relied on the original publications themselves rather than on summaries or commentaries. Such secondary sources were used to check the completeness of the review. The committee also reviewed the primary and secondary literature on basic toxicological and animal studies related to dioxin and other herbicides in question. Appendix A describes the committee's literature review strategy in detail.

Controversy has surrounded the study of Agent Orange since the first questions of herbicide-related health effects in Vietnam veterans were raised more than 20 years ago. In the course of its work, the committee heard allegations of scientific misconduct and claims of a government conspiracy to suppress information on health effects, as well as serious disagreements among scientists about the interpretation of laboratory and clinical data. The committee was not charged with investigating or resolving these controversies, and it did not attempt to do so. The committee took these issues into consideration only to the extent that they had a direct bearing on the scientific results that are the subject of this review.

We believe that the committee has produced a comprehensive, unbiased scientific review of the available evidence regarding potential health effects of exposure to herbicides in Vietnam veterans. Although the conclusions and recommendations presented here will not end the controversy surrounding this issue, it is the committee's hope that this report will crystallize the current scientific information on this important topic and prompt further research to answer the remaining questions being asked by veterans and their families, the Department of Veterans Affairs, and Congress.

The committee wishes to acknowledge that this study could not have been done without the assistance of a number of people, many of whom are listed in Appendix B. A special acknowledgement is extended to Donald Whorton and Albert Munson, both of whom served for a brief period with the committee. The work of the Institute of Medicine staff deserves high praise. Thanks are extended to the professional staff, Susan Rogers, Diane Mundt, Cynthia Abel, Catharyn Liverman, Gail Charnely, and Jane Durch, for their input, advice, and support. Thanks are also extended to Catherine Wesner, the study's project assistant, who planned travel and meeting arrangements and provided assistance with editorial changes to the manuscript; Jana Katz, the committee's student intern, who assisted with literature searches and in compiling the literature data base; Thomas Burroughs, who worked with IOM staff members in drafting several sections of the report; Zoe Schneider who aided in the preparation of the final

manuscript; Andrea Posner, who proofread the final changes in the manuscript; and Florence Poillon, who provided excellent editorial skills. Finally, the committee wishes to recognize the major contributions of the study director, Michael Stoto. It is through his expert leadership that this report has come to fruition.

Harold Fallon, Chairman
David Tollerud, Vice-chairman

Contents

Chapter 1: Executive Summary

INTRODUCTION	1
ORGANIZATION AND FRAMEWORK	2
CONCLUSIONS ABOUT HEALTH OUTCOMES	4
Health Outcomes with Sufficient Evidence of an Association	5
Health Outcomes with Limited/Suggestive Evidence of An Association	9
Health Outcomes with Limited/Suggestive Evidence of <u>No</u> Association	11
Health Outcomes with Inadequate/Insufficient Evidence to Determine Whether an Association Exists	11
Increased Risk in Vietnam Veterans	13
RESEARCH RECOMMENDATIONS	13
Epidemiologic Studies of Vietnam Veterans	14
Recommendation 1	14
Recommendation 2	15
Recommendation 3	16
Recommendation 4	16
Recommendation 5	16
Recommendation 6	17
Mandated Research Efforts	18

Chapter 2: History of the Controversy Over the Use of Herbicides

INTRODUCTION	1
MILITARY USE OF HERBICIDES IN VIETNAM	2
Herbicide Development and Testing	2
Use of Herbicides in Vietnam	4

Chapter 2 (continued)

EARLY CONCERNS ABOUT THE USE OF HERBICIDES IN VIETNAM	5
Early Accounts of Dioxin (TCDD)	5
Concerns over the Long-Term Use of Herbicides	6
CONCERNS ABOUT EXPOSURE TO AGENT ORANGE	8
Vietnam Veterans Return Home	8
The Beginning of the Controversy	9
AGENT ORANGE PRODUCT LIABILITY LITIGATION	10
Class Action Suit	10
CONCERNS ABOUT OTHER EXPOSURES TO 2,4,5-T AND TCDD	11
Occupational Exposure	12
Production Workers	12
Agricultural and Forestry Workers	12
Pulp and Paper Mill Workers	13
Major Event Associated with Occupational Exposure to Dioxin (TCDD) . .	13
Environmental Exposures	14
Domestic Use of Herbicides	14
Major Events Associated with Environmental Exposure to Dioxin	15
FEDERAL GOVERNMENT'S RESPONSE TO PUBLIC CONCERNS	19
White House	20
U.S. Congress	21
Hearings	21
Legislation on Agent Orange	21
Office of Technology Assessment	25
General Accounting Office	26
Department of the Air Force	27
Department of Veterans Affairs	27
Health Care	27
Research Efforts	28
Compensation and Benefits	28
Outreach Activities	29
Department of Health and Human Services	30
Centers for Disease Control	30
Environmental Protection Agency	32
RESPONSE BY OTHERS TO PUBLIC CONCERNS	33
State Governments	33
Veterans' Advocates	33
Australia and South Korea	34
National Research Council and Institute of Medicine	35
Studies Regarding Agent Orange in Vietnam	35

Chapter 3: The U.S. Military and the Herbicide Program in Vietnam

INTRODUCTION	1
MILITARY AND DEMOGRAPHIC CHARACTERISTICS OF	
VIETNAM VETERANS	1
Estimates of the Number of Military Personnel Serving in Vietnam	2
Federal Estimates	5
Other Survey Estimates	5
Military and Demographic Characteristics	6
Studies of Women Veterans	10
THE MILITARY USE OF HERBICIDES	11
Operation Ranch Hand	11
Herbicide Formulations	14
Military Herbicides	14
Level of Toxic Contaminants	17
Termination of the Program	18
Disposal of Surplus Herbicides	19
Ground Spraying of Herbicides	19
The HERBS and Services HERBS Tapes	21
Geographical Distribution of Herbicide Sprays	24
SUMMARY	32

Chapter 4: Toxicology

INTRODUCTION	1
OVERVIEW	4
Chemistry	4
Exposure and Metabolism	5
Carcinogenicity: TCDD	6
Mechanism of Action	6
Carcinogenicity: Herbicides	8
Mechanism of Action	10
Immunotoxicity: TCDD	10
Mechanism of Action	11
Immunotoxicity: Herbicides	11
Reproductive and Developmental Toxicity: TCDD	11
Mechanism of Action	12
Reproductive and Developmental Toxicity: Herbicides	12
Other Toxicity: TCDD	12
Other Toxicity: Herbicides	13

Chapter 4 (continued)

TOXICITY PROFILE OF TETRACHLORODIBENZO- <i>p</i> -DIOXIN	13
Introduction	13
Exposure and Pharmacokinetics	16
Bioavailability Following Various Routes of Exposure	16
Distribution	18
Metabolism	20
Excretion	21
Mechanism of Action	22
Introduction	22
Ah Receptor	23
Non-Ah Mediated Toxicity	26
Health Outcomes in Animal Studies	26
Carcinogenicity	26
Immunotoxicity	33
Hepatotoxicity	38
Reproductive and Developmental Toxicity	42
Neurotoxicity	45
Metabolic Toxicity	51
Gastrointestinal Toxicity	53
Respiratory Tract Associated Toxicity	54
Cardiovascular Toxicity	54
Corticosteroids	55
Dermal Toxicity	56
TOXICITY PROFILE OF 2,4-D	58
Introduction	58
Pharmacokinetics	58
Carcinogenicity	59
Genotoxicity	61
Acute Toxicity	61
Chronic Systemic Toxicity	62
Reproductive and Developmental Toxicity	62
Immunotoxicity	63
TOXICITY PROFILE OF 2,4,5-T	64
Introduction	64
Pharmacokinetics	64
Carcinogenicity	65
Genotoxicity	66
Acute Toxicity	66
Chronic Systemic Toxicity	66

Chapter 4 (continued)

Reproductive and Developmental Toxicity	67
Immunotoxicity	67
TOXICITY PROFILE OF CACODYLIC ACID	67
Introduction	68
Pharmacokinetics	68
Carcinogenicity	69
Genotoxicity	69
Acute Toxicity	70
Chronic Systemic Toxicity	70
Reproductive and Developmental Toxicity	70
Immunotoxicity	71
TOXICITY PROFILE OF PICLORAM	71
Introduction	71
Pharmacokinetics	71
Carcinogenicity	71
Genotoxicity	72
Acute Toxicity	72
Chronic Systemic Toxicity	73
Reproductive and Developmental Toxicity	73
Immunotoxicity	74

Chapter 5: Methodologic Considerations in Evaluating the Evidence

THE NATURE OF THE EVIDENCE	1
QUESTIONS TO BE ADDRESSED	3
Are Herbicides Statistically Associated with the Health Outcome?	3
What Is the Increased Risk of the Disease in Question	
Among Those Exposed to Herbicides in Vietnam?	4
BURDEN OF PROOF	5
CATEGORIES OF EVIDENCE	6
Experiments in Humans: Randomized Controlled Trials	6
Experiments in Animals: Animal Models	6
Controlled Epidemiologic Studies (Observational)	7
Cohort Studies	7
Proportionate Mortality Studies	10
Case-Control Studies	11
Case Reports and Case Series	13
Information from Death Certificates	14

Chapter 5 (continued)

Integration of Collective Results	14
Meta-Analysis	15
Considerations in Assessing the Strength of Scientific Evidence	16
Strength of Association	16
Dose-Response Relation	16
Temporally Correct Association	17
Consistency of Association	17
Specificity of Association	17
Biologic Plausibility	18
Other Considerations	18
The Role of Studies of Occupational and Environmental Exposures	18
NATURE OF THE CONCLUSIONS	19
Quantification	19
Resolution	19
Uncertainty and Confidence	20
Qualitative Aspects of the Review Process	21
Comprehensiveness	21
Neutrality	22
Judgment	22
SUMMARY OF THE EVIDENCE	22
Categories of Association	23
Increased Risk in Vietnam Veterans	23

Chapter 6: Exposure Assessment

INTRODUCTION	1
AN OVERVIEW OF EXPOSURE ASSESSMENT FOR EPIDEMIOLOGY	2
Hierarchy of Exposure Assessment Strategies	3
Exposure Assessment for Cohort Studies	5
Exposure Assessment for Case-Control Studies	6
Exposure Misclassification	7
Biomarkers	9
Biomarkers for TCDD	9
Chloracne as a Biomarker	11

Chapter 6 (continued)

EXPOSURE ASSESSMENT IN OCCUPATIONAL AND ENVIRONMENTAL STUDIES	12
Occupational Studies	12
Production Workers	13
Agricultural/Forestry/Outdoor Workers	14
Herbicide/Pesticide Sprayers	15
Paper and Pulp Mill Workers	15
Environmental Studies	16
Vietnamese Studies	17
Conclusions on Exposure Assessment in Occupational and Environmental Studies	17
EXPOSURE ASSESSMENT IN STUDIES OF VIETNAM VETERANS	18
Self-Reports	18
Records-Based Measures	19
Vietnam Service	19
Branch of Service	19
Combat Experience	20
Military Occupation	20
Reconstructing Estimated Exposure from Troop Location and Herbicide Spray Data	21
The CDC Exposure Opportunity Index	21
The CDC Agent Orange Study	22
The Stellmans' Study	25
Ranch Hand Exposure Index	26
Biomarkers of Exposure in Vietnam	26
CDC Agent Orange Validation Study (AOVS)	27
ESTIMATES OF EXPOSURE TO HERBICIDES AND TCDD DURING VIETNAM SERVICE	30
EXPOSURE RECONSTRUCTION	34
Development of the Exposure Reconstruction Model	34
Evaluation of the Exposure Reconstruction Model	36
SUMMARY	37

Chapter 7: Epidemiological Studies

INTRODUCTION	1
OCCUPATIONAL STUDIES	2
Production Workers	3
National Institute for Occupational Safety and Health	3
Monsanto	4
Dow	6
BASF	10
Other Chemical Plants	11
Agricultural/Forestry Workers	15
Cohort Studies	15
Case-Control Studies	22
Paper/Pulp Workers	34
Other Occupational Studies	35
ENVIRONMENTAL STUDIES	35
Seveso	35
Times Beach and Quail Run	50
Vietnam	52
Other Environmental Studies	54
VIETNAM VETERANS	57
United States	62
Ranch Hands	62
Centers for Disease Control	63
Department of Veterans Affairs	68
American Legion	74
State Studies	74
Other U.S. Vietnam Veteran Studies	79
Australia	80

Chapter 8: Cancer

INTRODUCTION	1
Cancer Epidemiology	2
Specific Issues with Regard to Herbicide Exposure in Vietnam	3
Exposure	4
Plausibility Data	4
Expected Number of Cancer Cases Among Vietnam Veterans	7

Chapter 8 (continued)

OVERALL CANCER	9
Background	9
Epidemiologic Studies	10
Occupational Studies	10
Environmental Studies	11
Vietnam Veterans Studies	11
Summary	12
GASTROINTESTINAL TRACT TUMORS	12
Background	12
Epidemiologic Studies	13
Summary	14
Conclusions	14
Strength of Evidence in Epidemiologic Studies	14
Biologic Plausibility	19
Increased Risk of Disease Among Vietnam Veterans	19
HEPATOBIILIARY CANCERS	19
Background	19
Epidemiologic Studies	20
Occupational Studies	20
Environmental Studies	21
Vietnam Veterans Studies	22
Summary	22
Conclusions	23
Strength of Evidence in Epidemiologic Studies	23
Biologic Plausibility	23
Increased Risk of Disease Among Vietnam Veterans	23
NASAL/NASOPHARYNGEAL CANCER	25
Background	25
Epidemiologic Studies	26
Conclusions	26
Strength of Evidence in Epidemiologic Studies	26
Biologic Plausibility	26
Increased Risk of Disease Among Vietnam Veterans	28
RESPIRATORY CANCERS	28
Background	28
Epidemiologic Studies	29
Occupational Studies	29
Environmental Studies	35
Vietnam Veterans Studies	37

Chapter 8 (continued)

Summary	38
Conclusions	40
Strength of Evidence in Epidemiologic Studies	40
Biologic Plausibility	40
Increased Risk of Disease Among Vietnam Veterans	40
BONE CANCER	40
Background	40
Epidemiologic Studies	41
Conclusions	43
Strength of Evidence in Epidemiologic Studies	43
Biologic Plausibility	43
Increased Risk of Disease Among Vietnam Veterans	43
SOFT TISSUE SARCOMAS	43
Background	43
Epidemiologic Studies	46
Occupational Studies	46
Environmental Studies	59
Vietnam Veterans Studies	60
Summary	65
Conclusions	66
Strength of Evidence in Epidemiologic Studies	66
Biologic Plausibility	67
Increased Risk of Disease Among Vietnam Veterans	67
SKIN CANCERS	67
Background	67
Epidemiologic Studies	69
Summary	69
Conclusions	71
Strength of Evidence in Epidemiologic Studies	71
Biologic Plausibility	71
Increased Risk of Disease Among Vietnam Veterans	71
CANCERS OF THE FEMALE REPRODUCTIVE SYSTEM AND BREAST	71
Background	71
Histopathology	72
Epidemiology	73
Epidemiologic Studies	74
Occupational Studies	75
Environmental Studies	77
Vietnam Veterans Studies	78

Chapter 8 (continued)

Conclusions	78
Strength of Evidence in Epidemiologic Studies	78
Biologic Plausibility	78
Increased Risk of Disease Among Vietnam Veterans	79
GENITOURINARY CANCERS	79
Background	79
Histopathology	79
Epidemiology	80
Epidemiologic Studies of Renal Cancer	81
Epidemiologic Studies of Bladder Cancer	82
Epidemiologic Studies of Prostate Cancer	82
Summary for Prostate Cancer	84
Epidemiologic Studies of Testicular Cancer	84
Summary for Testicular Cancer	87
Conclusions	87
Strength of Evidence in Epidemiologic Studies	87
Biologic Plausibility	87
Increased Risk of Disease Among Vietnam Veterans	87
BRAIN TUMORS	89
Background	89
Epidemiologic Studies	89
Summary	90
Conclusions	90
Strength of Evidence in Epidemiologic Studies	90
Biologic Plausibility	90
Increased Risk of Disease Among Vietnam Veterans	92
MALIGNANT LYMPHOMAS	92
Background	92
Histopathology	93
Epidemiology	93
Epidemiologic Studies of Non-Hodgkin's Lymphoma	95
Occupational Studies	95
Environmental Studies	107
Vietnam Veterans Studies	107
Summary for Non-Hodgkin's Lymphoma	114
Conclusions for Non-Hodgkin's Lymphoma	115
Strength of Evidence in Epidemiologic Studies	115
Biologic Plausibility	115
Increased Risk of Disease Among Vietnam Veterans	115

Chapter 8 (continued)

Epidemiologic Studies of Hodgkin's Disease	115
Occupational Studies	115
Vietnam Veterans Studies	119
Summary for Hodgkin's Disease	123
Conclusions for Hodgkin's Disease	124
Strength of Evidence in Epidemiologic Studies	124
Biologic Plausibility	124
Increased Risk of Disease Among Vietnam Veterans	124
Epidemiologic Studies of Multiple Myeloma	125
Occupational Studies	125
Environmental Studies	130
Vietnam Veterans Studies	130
Summary for Multiple Myeloma	130
Conclusions for Multiple Myeloma	131
Strength of Evidence in Epidemiologic Studies	131
Biologic Plausibility	131
Increased Risk of Disease Among Vietnam Veterans	131
LEUKEMIA	132
Background	132
Epidemiologic Studies	133
Occupational Studies	133
Environmental Studies	138
Vietnam Veterans Studies	138
Summary	138
Conclusions	138
Strength of Evidence in Epidemiologic Studies	138
Biologic Plausibility	139
Increased Risk of Disease in Vietnam Veterans	139
CHAPTER SUMMARY	139
Cancers with Sufficient Evidence of an Association	139
Cancers with Limited/Suggestive Evidence of An Association	141
Cancers with Limited/Suggestive Evidence of <u>No</u> Association	143
Cancers with Inadequate/Insufficient Evidence to Determine Whether an Association Exists	143
Increased Risk in Vietnam Veterans	144

Chapter 9: Reproductive Effects

INTRODUCTION	1
Methodologic Issues	1
Plausibility	2
SPONTANEOUS ABORTION	4
Introduction	4
Definition	4
Descriptive Epidemiology	5
Epidemiologic Studies of Spontaneous Abortion	5
Occupational Studies	5
Environmental Studies	7
Vietnamese Studies	7
Vietnam Veterans Studies	9
Summary	11
Conclusions	13
Strength of the Evidence in Epidemiologic Studies	13
Biologic Plausibility	13
Increased Risk of Disease in Vietnam Veterans	13
BIRTH DEFECTS	13
Introduction	13
Definition	13
Descriptive Epidemiology	14
Epidemiologic Studies of Birth Defects	15
Occupational Studies	15
Environmental Studies	15
Vietnam Veterans Studies	16
Summary	22
Conclusions	22
Strength of the Evidence in Epidemiologic Studies	22
Biologic Plausibility	22
Increased Risk of Disease in Vietnam Veterans	22
STILLBIRTH, NEONATAL DEATH, AND INFANT DEATH	25
Introduction	25
Definitions	25
Descriptive Epidemiology	25
Epidemiologic Studies of Stillbirth	26
Occupational and Environmental Studies	26
Vietnam Veterans Studies	27

Chapter 9 (continued)

Epidemiologic Studies of Neonatal Death	27
Occupational and Environmental Studies	27
Vietnam Veterans Studies	27
Epidemiologic Studies of Infant Death	28
Occupational and Environmental Studies	28
Vietnam Veterans Studies	28
Summary	28
Stillbirth and Neonatal Death	28
Infant Death	29
Conclusions	29
Strength of the Evidence in Epidemiologic Studies	29
Biologic Plausibility	29
Increased Risk of Disease in Vietnam Veterans	29
LOW BIRTHWEIGHT	32
Introduction	32
Definition	32
Descriptive Epidemiology	32
Epidemiologic Studies of Low Birthweight	32
Occupational and Environmental Studies	32
Vietnam Veterans Studies	33
Summary	33
Conclusions	35
Strength of the Evidence in Epidemiologic Studies	35
Biologic Plausibility	35
Increased Risk of Disease in Vietnam Veterans	35
CHILDHOOD CANCER	35
Introduction	35
Definition and Descriptive Epidemiology	35
Epidemiologic Studies of Childhood Cancer	36
Occupational and Environmental Studies	36
Vietnam Veterans Studies	36
Summary	37
Conclusions	37
Strength of the Evidence in Epidemiologic Studies	37
Biologic Plausibility	37
Increased Risk of Disease in Vietnam Veterans	37

Chapter 9 (continued)

SPERM PARAMETERS AND INFERTILITY	39
Introduction	39
Definition	39
Sperm Parameters	39
Infertility	39
Descriptive Epidemiology	39
Epidemiologic Studies of Sperm Parameters	40
Occupational and Environmental Studies	40
Vietnam Veterans Studies	40
Epidemiologic Studies of Infertility	40
Occupational and Environmental Studies	40
Vietnam Veterans Studies	40
Summary	41
Conclusions	41
Review of the Evidence in Epidemiologic Studies	41
Biologic Plausibility	41
Increased Risk of Disease in Vietnam Veterans	43

Chapter 10: Neurobehavioral Effects

INTRODUCTION	1
COGNITIVE AND NEUROPSYCHIATRIC EFFECTS	3
Epidemiologic Studies of Cognitive and Neuropsychiatric Effects	3
Occupational Studies	3
Environmental Studies	9
Vietnam Veterans Studies	11
Summary of Cognitive and Neuropsychiatric Effects	13
Conclusions for Cognitive and Neuropsychiatric Effects	14
Strength of Evidence in Epidemiologic Studies	14
Biologic Plausibility	14
Increased Risk of Disease Among Vietnam Veterans	14
MOTOR/COORDINATION DYSFUNCTION	15
Epidemiologic Studies of Motor/Coordination Dysfunction	15
Occupational Studies	15
Environmental Studies	15
Vietnam Veterans Studies	16
Summary of Motor/Coordination Dysfunction	17

Chapter 10 (continued)

Conclusions for Motor/Coordination Dysfunction	18
Strength of Evidence in Epidemiologic Studies	18
Biologic Plausibility	18
Increased Risk of Disease Among Vietnam Veterans	18
PERIPHERAL NERVOUS SYSTEM DISORDERS	18
Epidemiologic Studies of Peripheral Nervous System Disorders	18
Occupational Studies	18
Environmental Studies	20
Vietnam Veterans Studies	21
Summary of Peripheral Nervous System Disorders	21
Conclusions for Peripheral Nervous System Disorders	22
Strength of Evidence in Epidemiologic Studies	22
Biologic Plausibility	22
Increased Risk of Disease Among Vietnam Veterans	22

Chapter 11: Other Health Effects

INTRODUCTION	1
CHLORACNE	1
Epidemiologic Studies of Chloracne	2
Occupational Studies	2
Environmental Studies	4
Vietnam Veterans Studies	5
Summary for Chloracne	6
Conclusions for Chloracne	6
Strength of Evidence in Epidemiologic Studies	6
Biologic Plausibility	6
Increased Risk of Disease Among Vietnam Veterans	6
PORPHYRIA CUTANEA TARDA	7
Epidemiologic Studies of Porphyria Cutanea Tarda	8
Occupational Studies	8
Environmental Studies	8
Vietnam Veterans Studies	9
Summary for PCT	9
Conclusions for PCT	10
Strength of Evidence in Epidemiologic Studies	10
Biologic Plausibility	10
Increased Risk of Disease Among Vietnam Veterans	10

Chapter 11 (continued)

OTHER METABOLIC AND DIGESTIVE DISORDERS	10
Diabetes Mellitus	11
Epidemiologic Studies of Diabetes	11
Occupational and Environmental Studies	11
Vietnam Veterans Studies	12
Summary for Diabetes	12
Hepatic Enzymes	12
Epidemiologic Studies of Hepatic Enzymes	13
Occupational and Environmental Studies	13
Vietnam Veterans Studies	14
Summary for Hepatic Enzymes	14
Lipid Abnormalities	15
Epidemiologic Studies of Lipid Abnormalities	15
Occupational and Environmental Studies	15
Vietnam Veterans Studies	16
Summary for Lipid Abnormalities	16
Gastrointestinal Ulcers	17
Epidemiologic Studies of Ulcers	17
Occupational and Environmental Studies	17
Vietnam Veterans Studies	17
Summary for Ulcers	18
Conclusions for Other Metabolic and Digestive Disorders	18
Strength of Evidence	18
Biologic Plausibility	18
Increased Risk of Disease Among Vietnam Veterans	18
IMMUNE SYSTEM DISORDERS	19
Immune Modulation	19
Epidemiologic Studies of Immune Modulation	20
Occupational and Environmental Studies	20
Vietnam Veterans Studies	21
Autoimmunity	22
Epidemiologic Studies of Autoimmunity	23
Occupational and Environmental Studies	23
Vietnam Veterans Studies	23
Summary for Immune Disorders	24
Conclusions for Immune Disorders	24
Strength of the Evidence in Epidemiologic Studies	24
Biologic Plausibility	24
Increased Risk in Vietnam Veterans	25

Chapter 11 (continued)

CIRCULATORY DISORDERS	25
Epidemiologic Studies of Circulatory Disorders	25
Occupational Studies	25
Environmental Studies	26
Vietnam Veterans Studies	27
Summary for Circulatory Disorders	30
Conclusions for Circulatory Disorders	32
Strength of the Evidence	32
Biologic Plausibility	32
Increased Risk of Disease Among Vietnam Veterans	32
RESPIRATORY DISORDERS	32
Epidemiologic Studies of Respiratory Disorders	33
Occupational Studies	33
Environmental Studies	34
Vietnam Veterans Studies	34
Summary for Respiratory Disorders	35
Conclusions for Respiratory Disorders	36
Strength of the Evidence in Epidemiologic Studies	36
Biologic Plausibility	37
Increased Risk of Disease Among Vietnam Veterans	37

Chapter 12: Research Recommendations

INTRODUCTION	1
ANALYSES OF EXISTING DATA AND RESEARCH PROGRAMS	2
Studies of Highly Exposed Vietnam Veterans	2
Recommendation 1	2
FEASIBILITY OF NEW EPIDEMIOLOGIC STUDIES OF VIETNAM VETERANS	3
Recommendation 2	4
Recommendation 3	4
Recommendation 4	4
Recommendation 5	5
Recommendation 6	5
MANDATED RESEARCH EFFORTS	7
OTHER DIOXIN (TCDD)/HERBICIDE STUDIES	9

Appendices

- A. Literature Searches
- B. Presentations to the Committee and Outside Meetings
- C. Methodologic Observations on the Ranch Hand Study
- D. Committee and Staff Biographies
- E. Index to Epidemiologic Studies

Glossary

List of Acronyms and Abbreviations

Executive Summary

INTRODUCTION

Between 1962 and 1971, U.S. military forces sprayed nearly 19 million gallons of herbicides over approximately 3.6 million acres in Vietnam. The preparation known as Agent Orange accounted for approximately 11.2 million gallons of the total amount sprayed. Herbicides were used to strip the thick jungle canopy that helped conceal opposition forces, to destroy crops that enemy forces might depend upon, and to clear tall grass and bushes from around the perimeters of U.S. base camps and outlying fire support bases. Most large-scale spraying operations were conducted using airplanes and helicopters, but considerable quantities of herbicides were sprayed from boats and ground vehicles, as well as by soldiers wearing back-mounted equipment. Spraying began in 1962 and increased greatly in 1967. After a scientific report in 1969 concluded that one of the primary chemicals used in Agent Orange, namely, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) could cause birth defects in laboratory animals, U.S. forces suspended use of this herbicide in 1970 and halted all herbicide spraying in Vietnam the next year.

As the decade wore on, concern about possible long-term health consequences of Agent Orange and other herbicides heightened, fueled in particular by reports from growing numbers of Vietnam veterans that they had developed cancer or fathered handicapped children, which they attributed to wartime exposure to the herbicides. Along with the concerns of Vietnam veterans, public awareness increased because of reports of health concerns surrounding occupational and environmental exposure to dioxin--more specifically, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), informally known as TCDD--a contaminant of 2,4,5-T. Thousands of scientific studies have since been conducted, numerous government hearings have been held, and veterans organizations have pressed for conclusive answers, but the question of the health effects of herbicide exposure in Vietnam remains shrouded in controversy and mistrust. Indeed some veterans organizations, researchers, and public interest organizations remain skeptical that the issue has received full and impartial consideration by the Department of Veterans Affairs (DVA; formerly the Veterans Administration) and other federal agencies.

Faced with this lingering uncertainty and demands that the concerns of veterans be adequately addressed, the U.S. Congress passed Public Law 102-4, the "Agent Orange Act of 1991." This legislation directed the Secretary of Veterans Affairs to request that the National

Academy of Sciences conduct a comprehensive review and evaluation of available scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and their components, including dioxin.

In February 1992, the Institute of Medicine (IOM) of the National Academy of Sciences signed an agreement with the DVA to review and summarize the strength of the scientific evidence concerning the association between herbicide exposure during Vietnam service and each disease or condition suspected to be associated with such exposure. The IOM was also asked to make recommendations concerning the need, if any, for additional scientific studies to resolve areas of continuing scientific uncertainty and to comment on four particular programs mandated in Public Law 102-4.

To carry out the study, the IOM established the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. In conducting its study, the committee operated independently of the DVA and other government agencies. The committee was not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure; this was not part of its congressional charge. Rather, the study provides scientific information for the Secretary of Veterans Affairs to consider as the DVA exercises its responsibilities to Vietnam veterans.

ORGANIZATION AND FRAMEWORK

The framework for this report reflects the size and complexity of the committee's task. The committee felt that an evaluation of the health effects of exposure to herbicides in Vietnam veterans would not be complete without a historical review of the Agent Orange controversy. The report begins in Chapter 2 by tracing more than two decades of public concern about the military use of herbicides during the war in Vietnam, in addition to public concern over various environmental and occupational exposures to herbicides and dioxin that arose in parallel to veterans' concerns, and describes federal and state responses to this national dilemma.

Chapter 3 provides background information on the nature and extent of potential exposure of Vietnam veterans to herbicides, based on information about the military herbicide program. Some 3 million military personnel served in or near Vietnam, and as one historian notes, "there was no 'typical' U.S. soldier in Vietnam . . . Americans who served there went through many varied experiences--partly because the quality of the war varied in different areas of the country, and partly because the nature changed over time" (Karnow, 1991). Individual experiences also varied by branch of service, military occupation, rank, and type of military unit. As reflected in military records, the use of herbicides was varied as well. Starting in 1962 and peaking in the late 1960s, seven different herbicide formulations were used in varying quantities for a variety of purposes in different parts of the country; approximately 65 percent of these herbicides were contaminated by TCDD, in varying concentrations. Aerial spraying of herbicides by Operation Ranch Hand accounted for approximately 86 percent of all spraying and was well documented; other spraying by helicopters and from trucks or backpacks was poorly documented.

Chapter 4 provides toxicological background on the biologic plausibility of health effects that may occur in humans after accidental or occupational exposure to herbicides and TCDD components. This chapter describes the biological and chemical properties of the compounds in question as determined by basic research and animal studies. TCDD administered to laboratory animals interacts with an intracellular protein called the Ah receptor. This interaction appears to play a role in a number of health effects observed in animals. Because humans also have intracellular proteins that have been identified as Ah receptors, it is plausible that interactions between TCDD and these receptors could play a role in human health effects. In contrast to TCDD, the effects of the herbicides do not appear to be mediated through interactions with intracellular receptors. TCDD has also been shown to have a wide range of effects in laboratory animals on growth regulation, hormone systems, and other factors associated with the regulation of activities in normal cells. In addition, TCDD has been shown to cause cancer in laboratory animals at a variety of sites. If TCDD has similar effects on cell regulation in humans, it is plausible that it could have an effect on human cancer incidence. In contrast to TCDD, there is no convincing evidence in animals of, or mechanistic basis for, carcinogenicity or other health effects of any of the herbicides, although they have not been studied as extensively as TCDD.

In fulfilling its charge of judging whether each of a set of human health effects is associated with exposure to herbicides or dioxin, most of the committee's efforts concentrated on reviewing and interpreting epidemiologic studies. The committee began its evaluation presuming neither the existence nor the absence of association. It has sought to characterize and weigh the strengths and limitations of the available evidence. These judgments have both quantitative and qualitative aspects. They reflect the nature of the exposures, health outcomes, and populations at issue; the characteristics of the evidence examined; and the approach taken to evaluate that evidence. To facilitate independent assessment of the committee's conclusions, Chapter 5 describes as explicitly as possible the methodological considerations that guided the committee's review and its process of evaluation.

In reviewing the literature, the committee discerned that the existing epidemiologic data base is severely lacking in quantitative measures of individual exposure to herbicides and dioxin. Assessment of the intensity and duration of individual exposures is a key component in determining whether specific health outcomes are associated with exposure to dioxin or other chemicals found in the herbicides used in Vietnam. Although different approaches have been used to estimate exposure in Vietnam veterans and in others exposed occupationally or environmentally, each approach is limited in its ability to determine precisely the degree and level of individual exposure. The problems associated with each of these approaches are discussed in detail in Chapter 6. New biochemical techniques that can detect small amounts of TCDD in the blood many years after exposure have some merit, especially for detecting *group* differences. However, because of common background exposure of all Americans to TCDD, poorly understood variations among individuals in TCDD metabolism, and relatively large measurement errors, *individual* TCDD serum levels are usually not meaningful. Furthermore, because not all herbicides used in Vietnam contained TCDD, serum TCDD levels are not good indicators of overall exposure to herbicides. Chloracne has been used in epidemiologic studies

as a biomarker for TCDD exposure, but the data indicate that it is neither sensitive nor specific. It is usually not long lasting, is difficult to diagnose, and is not at all sensitive to exposure to herbicides that are not contaminated with TCDD.

Although definitive data are lacking, the available quantitative and qualitative evidence about herbicide exposure summarized in Chapter 6 suggests that Vietnam veterans as a group had substantially lower exposure to herbicides and dioxin than the subjects in many occupational studies. The participants in Operation Ranch Hand are an exception to this pattern, and it is likely that others among the approximately 3 million men and woman who served in Vietnam were exposed to herbicides at levels associated with health effects. Thus, in the committee's judgment, a sufficiently large range of exposures may exist among Vietnam veterans to conduct a valid epidemiologic study for certain health outcomes (see research recommendations below).

Due, in part, to the uncertain validity of exposure measurements in many of the studies of veterans, the committee decided to review studies of other groups potentially exposed to the herbicides used in Vietnam and TCDD, especially phenoxy herbicides, including 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-T, chlorophenols, and other compounds. These groups include chemical production and agricultural workers, residents of Vietnam, and people exposed heavily to herbicides or dioxins as a result of residing near the site of an accident or a toxic waste dumping area. The committee felt that considering studies of other groups could help address the issue of whether these compounds might be associated with particular health outcomes, even though these results would have only an indirect bearing on the increased risk of disease in veterans themselves. Some of these studies, especially those of workers in chemical production plants, provide stronger evidence about health effects than studies of veterans because exposure was generally more easily quantified and measured. Furthermore, the general level and duration of exposure to the chemicals were greater and the studies were of sufficient size to examine the health risks among those with varying levels of exposure.

Because the committee relied on many of the same epidemiologic studies when assessing potential associations with various health effects, Chapter 7 provides a framework for the methods used in the epidemiologic studies on which the committee based its report. The nature of the exposure to herbicides and herbicide components varied substantially for each; therefore, both the organization of the chapter (which is structured to reflect similarities and differences in the populations studied) and the methodologic issues that are summarized for each study emphasize exposure.

CONCLUSIONS ABOUT HEALTH OUTCOMES

Chapters 8 through 11 provide a detailed review of the epidemiologic studies evaluated by the committee and their implications for cancer, reproductive, neurobehavioral, and other health effects. The committee's specific mandate was to determine, if possible,

1. whether there is a statistical association between the suspect diseases and herbicide use, taking into account the strength of the scientific evidence and the appropriateness of the methods used to detect the association;
2. the increased risk of disease among individuals exposed to herbicides during service in Vietnam; and
3. whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and a disease.

As detailed in Chapter 5, the committee addressed the first part of this charge by assigning each of the health outcomes under study into one of the four categories listed in Table 1-1 on the basis of the epidemiologic evidence that it reviewed. The specific rationale for each of the findings summarized in this table is given in Chapters 8 through 11. The second part of the charge is addressed at the end of this section. The committee's response to the third part of the charge is summarized in general terms in Chapter 4, and specific findings for each health outcome are also given in Chapters 8 through 11.

The definitions of the categories and the criteria for assigning a particular health outcome to them are described in Table 1-1. Consistent with the charge to the Secretary of Veterans Affairs in Public Law 102-4, the distinctions between categories are based on "statistical association," not on causality, as is common in scientific reviews. The committee was charged with reviewing the scientific evidence, rather than making recommendations regarding DVA policy, and Table 1-1 is not intended to imply or suggest any policy decisions, which must rest with the Secretary.

Health Outcomes with Sufficient Evidence of an Association

The committee found sufficient evidence of an association with herbicides and/or TCDD for three cancers: soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. For cancers in this category, a positive association between herbicides and the outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regards evidence from several small studies that are free from bias and confounding, and show an association that is consistent in magnitude and direction, as sufficient evidence for an association.

Soft tissue sarcomas are a rare but diverse group of tumors that share a common International Classification of Diseases code but have a wide variety of forms and causes. The strongest evidence for an association between STS and exposure to phenoxy herbicides comes from a series of case-control studies involving a total of 506 cases conducted by Hardell and colleagues in Sweden (Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell and Eriksson, 1988; Eriksson et al., 1990) that show an association between STS and exposure to

TABLE 1-1 Summary of Findings in Occupational, Environmental, and Veterans Studies Regarding the Association Between Specific Health Problems and Exposure to Herbicides

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence for an association. There is sufficient evidence of an association between exposure to herbicides and the following health outcomes:

- Soft tissue sarcoma
- Non-Hodgkin's lymphoma
- Hodgkin's disease
- Chloracne
- Porphyria cutanea tarda (in genetically susceptible individuals)

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent. There is limited/suggestive evidence of an association between exposure to herbicides and the following health outcomes:

- Respiratory cancers (lung, larynx, trachea)
- Prostate cancer
- Multiple myeloma

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and the following health outcomes:

- Hepatobiliary cancers
- Nasal/nasopharyngeal cancer
- Bone cancer
- Female reproductive cancers (breast, cervical, uterine, ovarian)
- Renal cancer
- Testicular cancer
- Leukemia
- Spontaneous abortion
- Birth defects
- Neonatal/infant death and stillbirths
- Low birthweight
- Childhood cancer in offspring
- Abnormal sperm parameters and infertility

TABLE 1-1 (continued)

Inadequate/Insufficient Evidence to Determine Whether an Association Exists (continued)

Cognitive and neuropsychiatric disorders
Motor/coordination dysfunction
Peripheral nervous system disorders
Metabolic and digestive disorders (diabetes, changes in liver enzymes,
lipid abnormalities, ulcers)
Immune system disorders (immune modulation and autoimmunity)
Circulatory disorders
Respiratory disorders

Limited/Suggestive Evidence of No Association

Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. *In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.* There is limited/suggestive evidence of *no* association between exposure to herbicides and the following health outcomes:

Skin cancer
Gastrointestinal tumors (stomach cancer, pancreatic
cancer, colon cancer, rectal cancer)
Bladder cancer
Brain tumors

NOTE: "Herbicides" refers to the major herbicides used in Vietnam: 2,4-D (2,4-dichlorophenoxyacetic acid); 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and its contaminant TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin); cacodylic acid; and picloram. The evidence regarding association is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

phenoxy herbicides, chlorophenols, or both. Although these studies have been criticized, the committee feels that there is insufficient justification to discount the consistent pattern of elevated risks, and the clearly described and sound methods employed. These findings are supported by a significantly increased risk in the NIOSH study (SMR=9.2, CI 1.9-27.0) for the production workers most highly exposed to TCDD (Fingerhut et al., 1991), and a similar increased risk in the IARC cohort (SMR=6.1, CI 1.7-15.5) for deaths that occurred between 10 and 19 years after the first exposure (Saracci et al., 1991). These are the two largest, as well as the most highly exposed occupational cohorts. Some studies in other occupational, environmental, and veterans groups showed an increased risk for STS, but the results were commonly nonsignificant possibly because of small sample sizes related to the relative rarity of STS in the population. Because of difficulties in diagnosing this group of tumors, the epidemiologic studies reviewed by the committee were inconsistent with regard to the specific types of tumors included in the analyses. The available data did not permit the committee to determine whether specific forms of STS were or were not associated with TCDD and/or herbicides. Therefore, the committee's findings relate to the class as a whole.

Non-Hodgkin's lymphoma includes a group of malignant lymphomas, that is, neoplasms derived from lymphoreticular cells in lymph nodes, bone marrow, spleen, liver, or other sites in the body. One large, well-conducted case-control study in Sweden by Hardell and colleagues (1981) examined NHL and Hodgkin's disease together and found an odds ratio of 6.0 (CI 3.7-9.7) based on 105 cases for exposure to phenoxy acids or chlorophenols, and these results held up under further investigation of the validity of exposure assessment and other potential biases (Hardell, 1981). A more recent case-control study by Persson and colleagues (1989) showed increased risk for NHL in those exposed to phenoxy acids (OR=4.9, CI 1.0-27.0), based on a logistic regression analysis of 106 cases. Other studies of farmers and agricultural workers are generally positive for an association between NHL and herbicides/TCDD; however, only some are significant. All of the studies of U.S. agricultural workers reviewed showed elevated relative risks (although none were significant), and two NCI studies of farmers in Kansas and Nebraska (Hoar et al., 1986; Zahm et al., 1990) show patterns of increased risk linked to use of 2,4-D. The CDC Selected Cancers Study found an increased risk of NHL in association with service in Vietnam; other studies of veterans, generally with small sample sizes, are consistent with an association. In contrast, studies of production workers, including the largest, most heavily exposed cohorts (Fingerhut et al., 1991; Saracci et al., 1991; Zober et al., 1990; Manz et al., 1991) indicate no increased risk. Thus, unlike most of the other cancers studied by the committee for which the data do not distinguish between the effects of herbicides and TCDD, the available epidemiologic data suggest that the phenoxy herbicides, including 2,4-D, rather than TCDD may be associated with non-Hodgkin's lymphomas.

Hodgkin's disease, also a malignant lymphoma, is a neoplastic disease characterized by progressive anemia and enlargement of lymph nodes, spleen, and liver. Fewer studies have been conducted of HD in relation to exposure to herbicides or TCDD than have been conducted of STS or NHL, but the pattern of results is strikingly consistent. The 60 HD cases in the study by Hardell and colleagues (1981) were later examined by Hardell and Bengtsson (1983),

who found odds ratios of 2.4 (CI 0.9-6.5) for low-grade exposure to chlorophenols and 6.5 (CI 2.7-19.0) for high-grade exposures. Persson and colleagues' study (1989) of 54 HD cases showed a large, but not statistically significant, OR=3.8 (CI 0.5-35.2) for exposure to phenoxy acids. Furthermore, nearly all of the 13 case-control and agricultural worker studies show increased risk for HD, although only a few of these results are statistically significant. As with NHL, even the largest studies of production workers exposed to TCDD do not indicate an increased risk. The few studies of HD in Vietnam veterans tend to show elevated risks, all but one are not statistically significant.

When these three cancers (STS, NHL, and HD) are considered as a whole, it is noteworthy that the strongest evidence for an association with exposure to phenoxy herbicides is the series of case-control studies conducted by Hardell and colleagues and the cohort studies of herbicide applicators and agricultural workers. Studies in other countries are sometimes positive, but not as consistently. Whether this reflects higher typical exposure levels in workers in the countries studied, genetic differences in susceptibility to these diseases, the fact that more intensive studies have taken place, or other risk factors is not known. With regard to STS, the study of Woods and colleagues (1987) suggests that both exposure levels and genetic differences are at play. However, although there may be differences from population to population in the increased risk associated with exposure to herbicides and TCDD, the committee regards the available evidence as sufficient to indicate that there is a statistical association between the herbicides used in Vietnam and STS, NHL, and HD.

The other two health outcomes for which the committee found sufficient evidence of an association with herbicides or TCDD are both skin conditions (see Chapter 11). Chloracne is a specific acne-like skin disorder characterized by exposure to TCDD or related chemicals (but not herbicides). Porphyria cutanea tarda (PCT), which is characterized by thinning and blistering of the skin in sun-exposed areas, is an uncommon disease in which porphyrins are abnormally metabolized. Only genetically predisposed individuals have been shown to develop PCT after TCDD exposure. Both chloracne and PCT have been shown in animal and human studies to be associated with TCDD per se. The clinical evidence for these conditions suggests that onset occurs soon after exposure to TCDD; however, the conditions subside (although perhaps slowly) after exposure ceases.

Health Outcomes with Limited/Suggestive Evidence of An Association

The committee found limited/suggestive evidence of an association for three other cancers: respiratory cancers, prostate cancer, and multiple myeloma. For outcomes in this category, the evidence must be suggestive of an association between herbicides and the outcome, but may be limited because chance, bias, or confounding could not be ruled out with confidence. Typically, at least one high-quality study indicates a positive association, but the results of other studies may be inconsistent.

Among the many epidemiologic studies of respiratory cancers (specifically cancers of the lung, larynx, and trachea), positive associations were found consistently only in those studies in

which TCDD or herbicide exposures were probably high and prolonged, especially the largest, most heavily exposed cohorts of chemical production workers exposed to TCDD (Zober et al., 1990; Fingerhut et al., 1991; Manz et al., 1991; Saracci et al., 1991) and herbicide applicators (Axelson and Sundell, 1974; Riihimaki et al., 1982; Blair, 1983; Green, 1991). Studies of farmers tended to show a decreased risk of respiratory cancers (perhaps due to lower smoking rates), and studies of Vietnam veterans are inconclusive. The committee felt that the evidence for this association was limited/suggestive rather than sufficient because of the inconsistent pattern of positive findings across populations with various degrees of exposure and because the most important risk factor for respiratory cancers--cigarette smoking--was not fully controlled for or evaluated in all studies.

Several studies have shown elevated risk for prostate cancer in agricultural or forestry workers. In a large cohort study of Canadian farmers (Morrison et al., 1993), an increased risk of prostate cancer was associated with herbicide spraying, and increasing risk was shown with increasing number of acres sprayed. For the entire cohort, the relative risk for prostate cancer and spraying at least 250 acres was 1.2 (CI 1.0-1.5). When the analysis was restricted to the farmers most likely to be exposed to phenoxy herbicides or other herbicides, and those with no employees, no custom workers to do the spraying for them, and age between 45-69 years, the test for trend over increasing number of acres sprayed was significant. The risk was elevated a study of USDA forest conservationists (OR=1.6, CI 0.9-3.0) (Alavanja et al., 1989), and a case-control study of white male Iowans who died of prostate cancer (Burmeister et al., 1983) found a significant association (OR=1.2) that was not associated with any particular agricultural practice. These results are strengthened by a consistent pattern of nonsignificant elevated risks in studies of chemical production workers in the United States and other countries, agricultural workers, pesticide applicators, paper and pulp workers, and the Seveso population. Studies of prostate cancer among Vietnam veterans or following environmental exposures have not consistently shown an association. However, prostate cancer is generally a disease of older men, and the risk among Vietnam veterans would not be detectable in published epidemiologic studies. Because there was a strong indication of a dose-response relationship in one study and a consistent positive association in a number of others, the committee felt that the evidence for association with herbicide exposure was limited/suggestive for prostate cancer.

Multiple myeloma, a cancer of specific bone marrow cells, has been less extensively studied than other lymphomas, but a consistent pattern of elevated risks appears in the studies that have been conducted. Ten studies of agricultural and forestry workers provide information on MM risk in relation to herbicide or pesticide exposure. All demonstrated an odds ratio or SMR greater than 1.0; seven did so at a statistically significant level. This finding is made more specific for herbicide exposure by subanalyses in four of these studies (Burmeister et al., 1983; Cantor and Blair, 1984; Alavanja et al., 1989; Boffetta et al., 1989) that suggest higher risks for those exposed to herbicides, and higher risks for the studies of herbicide applicators (Riihimaki et al., 1983; Swaen et al., 1992). The committee determined that the evidence for this association was limited/suggestive because the individuals in the existing studies--mostly farmers--have, by the nature of their occupation, probably been exposed to a range of

potentially carcinogenic agents other than herbicides and TCDD. Multiple myeloma, like non-Hodgkin's lymphoma and Hodgkin's disease for which there is stronger epidemiologic evidence of an association, is derived from lymphoreticular cells, which adds to the biologic plausibility of an association.

Health Outcomes with Limited/Suggestive Evidence of No Association

For a small group of cancers the committee found a sufficient number and variety of well-designed studies to conclude that there is limited/suggestive evidence of *no* association between these cancers and TCDD or the herbicides under study. This group includes gastrointestinal tumors (colon, rectal, stomach, and pancreatic), skin cancer, brain tumors, and bladder cancer. For outcomes in this category, several adequate studies covering the full range of levels of exposure that human beings are known to encounter are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure, and which have relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

The data on colon cancer exemplify the situation that led the committee to say that there was evidence of no association between a cancer and exposure to herbicides and/or TCDD. Colon cancer is relatively common, so an increase in the risk of these cancers would be relatively easy to detect in occupational studies. The epidemiologic studies reviewed by the committee that address colon cancer include a mixture of occupational studies of various types, environmental studies, and studies of Vietnam veterans. Some of the studies such as the NIOSH (Fingerhut et al., 1991) and IARC (Saracci et al., 1991) cohorts are large and have relatively high exposures. The number of studies with estimated relative risks above and below 1.0 are roughly evenly distributed, and a number of studies have tight confidence intervals that include 1.0. The NIOSH study, for instance, based on 25 exposed cases, finds an odds ratio of 1.2 with a 95 percent confidence interval of 0.8 to 1.8. The IARC study finds an odds ratio of 1.1 (CI 0.8-1.5) based on 41 cases. Thus, this pattern suggests that there is no association between herbicides/TCDD and colon cancer, at least in the situations represented in the available studies.

Health Outcomes with Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The scientific data for the remainder of the cancers and other diseases reviewed by the committee were inadequate or insufficient to determine whether an association exists. For cancers in this category, the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association.

For example, studies fail to control for confounding or have inadequate exposure assessment.

This group includes hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers (breast, cervical, uterine, ovarian), renal cancer, testicular cancer, and leukemia. For example, there are relatively few occupational, environmental, or veterans studies of liver cancer, and most of these are small in size and have not controlled for life-style-related risk factors. One of the largest studies (Hardell et al., 1984) indicates an increased risk for liver cancer and exposure to herbicides, but another study of Swedish agricultural workers (Wiklund, 1983) estimates a relative risk that is significantly less than 1.0. The estimated relative risks from other studies are both positive and negative. As a whole, when bearing in mind the methodological difficulties associated with most of the few existing studies, the evidence regarding liver cancer is not convincing about either an association with herbicides/TCDD or the lack of an association.

The epidemiologic evidence for an association between exposure to herbicides and leukemia comes primarily from studies of farmers and residents of Seveso, Italy. The observed overall relative risk for leukemia mortality and incidence in Seveso was elevated, but not significantly. A number of studies of farmers that the committee found convincing for NHL, HD, or MM also show a consistently elevated risk of leukemia, but these results are not necessarily due to herbicide use because confounding exposures were not controlled for adequately in the analyses of these studies and because when farmers are stratified by suspected use of herbicide, the incidence of leukemia is generally not elevated. Some studies of chemical workers found an increased risk of leukemia, but the number of cases was small in all of these studies. The available data on Vietnam veterans are generally not conclusive because the exposure data are inadequate for the cohort being studied. Small sample sizes weaken the studies of the Ranch Hands or Chemical Corps, where excesses are not likely to be detected.

A number of occupational, environmental, and Vietnam veteran studies were available for assessing the association between herbicide and TCDD exposures and reproductive outcomes. These studies generally reported no association with any of the reproductive outcomes examined by the committee--spontaneous abortion, birth defects, stillbirth, neonatal and infant death, low birthweight, childhood cancer, or altered sperm parameters and infertility. However, given the small sample sizes, the lack of consistent findings, and inadequate exposure classification in most studies, the evidence is considered inadequate for determination of an association.

Studies of neurotoxic effects of herbicides or TCDD were also inadequate for determining whether an association exists between exposures and chronic cognitive or neuropsychiatric disorders, motor/coordination dysfunction, and peripheral nervous system disorders. As a group the studies have not applied uniform operational definitions of neurobehavioral disorders. Information on individual exposure was often inadequate and complicated by exposure to multiple chemicals, and only a limited number of studies provided sufficient comparison group data. Reported abnormalities have ranged from mild and reversible to severe and chronic. While the chances of detecting subtle central nervous system disorders 20 years after exposure are small given the assessment tools currently available, the committee recognized that it may be possible for subtle changes that occurred earlier in life to manifest themselves in later adult

life when compounded by the normal aging process. Therefore, while the currently available evidence is insufficient, study of the interactive effects of exposure to herbicides and TCDD with age on neurobehavioral functioning are encouraged. In addition, observations from followup of veterans and some environmental studies warrant further investigation of motor/sensory/coordination problems in exposed persons.

Other health effects examined by the committee for which the evidence was determined to be insufficient included several metabolic and digestive disorders (diabetes, changes in liver enzymes, lipid abnormalities, and gastrointestinal ulcers), immune system disorders, and circulatory and respiratory disorders. Assessment of these disorders in association with herbicides and TCDD involved the medical evaluation of a wide array of critical signs and symptoms, laboratory parameters, and other diagnostic tools. Studies of these health effects were limited by poor exposure measures, generally small sample sizes, and the lack of assessment of independent risk factors for certain outcomes, such as smoking and certain circulatory and respiratory disorders, or alcohol use and ulcers.

Increased Risk in Vietnam Veterans

Although there have been numerous health studies of Vietnam veterans, most have been hampered by relatively poor measures of exposure to herbicides or TCDD, in addition to other methodological problems. In Table 1-1, most of the evidence on which the findings are based comes from studies of people exposed to dioxin or herbicides in occupational and environmental settings, rather than from studies of Vietnam veterans. The committee found this body of evidence sufficient for reaching the conclusions about statistical associations between herbicides and health outcomes summarized in Table 1-1; however, the lack of adequate data on Vietnam veterans per se complicates the second part of the committee's charge, which is to determine the increased risk of disease among individuals exposed to herbicides during service in Vietnam. To estimate the magnitude of risk for a particular health outcome among herbicide-exposed Vietnam veterans, quantitative information about the dose-time-response relationship for each health outcome in humans, information on the extent of herbicide exposure among Vietnam veterans, and estimates of individual exposure are needed. Given the large uncertainties that remain about the magnitude of potential risk from exposure to herbicides in the studies that have been reviewed (Chapters 8-11), the inadequate control for important confounders, and the uncertainty about the nature and magnitude of exposure to herbicides in Vietnam (Chapter 6), none of the ingredients necessary for a quantitative risk assessment are available. Thus, it is not possible for the committee to quantify the degree of risk likely to be experienced by veterans because of their exposure to herbicides in Vietnam. The available quantitative and qualitative evidence about herbicide exposure among various groups studied suggests that Vietnam veterans as a group (except those with documented high exposures, such as participants in Operation Ranch Hand) had lower exposure to herbicides and TCDD than the subjects in many occupational and environmental studies. However, individual

veterans who had very high exposures to herbicides could have risks approaching those in the occupational and environmental studies.

RESEARCH RECOMMENDATIONS

The committee was also asked to make recommendations concerning the need, if any, for additional scientific studies to resolve areas of continuing scientific uncertainty concerning the health effects of the herbicides used in Vietnam. Based on its review of the available epidemiologic evidence and a consideration of the quality of exposure information available in existing studies, especially of Vietnam veterans, the committee concluded that a series of epidemiologic studies of veterans could yield valuable information if a new, valid exposure reconstruction model could be developed. The committee also sees value in continuing the existing Ranch Hand study and expanding it to include Army Chemical Corps veterans. The committee's research recommendations emphasize studies of Vietnam veterans, rather than general toxicologic or epidemiologic studies of occupationally or environmentally exposed populations. A substantial amount of research on the toxicology and epidemiology of herbicides and herbicide components is already under way in the United States and abroad. Indeed, many of the studies on which the committee's conclusions are based have been published since 1991. Although not targeted specifically to Vietnam veterans, it is likely that this research will also contribute to the knowledge of potential health effects in this population.

Epidemiologic Studies of Vietnam Veterans

The committee makes the following recommendations regarding epidemiologic studies of Vietnam veterans.

Recommendation 1. The committee endorses continued follow-up of the Air Force Ranch Hand cohort and its comparison group, and recommends that members of the Army Chemical Corps and an appropriate comparison group be followed in a similar study. An independent, nongovernmental scientific panel should be established to review and approve a new, expanded research protocol for both study populations, and to commission and direct a common analysis of the results.

Much can be learned by reanalysis of existing data or more in-depth analysis of data expected from current research programs investigating the health of Vietnam veterans, including the Air Force Ranch Hand study and DVA studies of other highly exposed Vietnam veterans such as members of the Chemical Corps. Priorities for specific health outcomes are

discussed after recommendation 6. Public perception of the federal government's interest in the outcome of these studies suggests the need for studies of the health of Vietnam veterans to be conducted by a nongovernmental organization. Ranch Hand's excellent participation rate argues that components of the Department of Defense or the DVA continue to conduct follow-up examinations of the Ranch Hand and Army Chemical Corps cohorts. However, an independent, nongovernmental scientific panel is needed to oversee the analyses of resulting data in order to satisfy the public's concern about impartiality and scientific credibility.

As discussed in Chapter 6, one of the major problems with the interpretation of existing studies is the frequent lack of appropriate measures of exposure to herbicides or TCDD; however, the committee finds that it may be possible to develop better exposure measures for Vietnam veterans. In particular, Chapter 6 proposes measures that are not dependent on serum TCDD levels (which the committee finds inappropriate for the full range of herbicide exposures) but instead recommends the use of less formal sources of historical information about base perimeter spraying and other relevant exposures, as discussed below in Recommendation 4. Thus, the committee concludes that certain further research efforts using new measures of exposure to herbicides in Vietnam are both necessary and potentially feasible. However, each of the possible measures that the committee has considered involves some degree of nondifferential misclassification bias, and the effect of this bias on risk estimates would likely be to underestimate true effects if they existed, possibly to the point that they would not be detected. In particular, the committee recommends that the following steps be taken prior to undertaking new epidemiologic studies of Vietnam veterans, for the reasons described below.

Recommendation 2. The Department of Defense and the Department of Veterans Affairs should identify Vietnam service in the computerized index of their records.

Chapter 3 notes that Vietnam service is not a "flagged item" on the computerized index of military personnel records archived at the National Personnel Records Center, which is maintained by the General Services Administration, under an agreement with the Department of Defense, in St. Louis, Missouri. Therefore, the computerized index of the record system does not allow for searches or selection of records of individuals who have served in Vietnam. The lack of an indicator of Vietnam service complicates every epidemiologic study of veterans based on military records and leads to methodologic inconsistencies among studies in defining the population under consideration. Adding this indicator to the computerized data base would facilitate future mortality studies based on computerized records, thereby increasing accuracy and decreasing cost, and would also simplify other epidemiologic studies of health outcomes in Vietnam veterans. All servicemen and women who were stationed in Vietnam or in the Vietnam theater during the Vietnam era should be identified in the records.

Recommendation 3. Biomarkers for herbicide exposure should be developed further.

Considerable uncertainty remains about the use of current or future serum TCDD levels as indicators of past exposure to dioxin in Vietnam veterans. Further research on the toxicokinetics of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) is needed to permit more accurate extrapolation from current serum TCDD measurements to past exposures. Development of new biomarkers for exposure to herbicides, per se, also would be useful.

Recommendation 4. A nongovernmental organization with appropriate experience in historical exposure reconstruction should be commissioned to develop and test models of herbicide exposure for use in studies of Vietnam veterans.

Exposure assessment has been a weak aspect of most epidemiologic studies of Vietnam veterans. The military reports and personal testimony reviewed by the committee suggest that a sufficient range of exposure to herbicides may exist among Vietnam veterans for valid epidemiologic studies of certain health outcomes, and the committee believes that it is possible to develop valid exposure reconstruction models for such studies by using the methods of historical exposure reconstruction. Historical exposure reconstruction requires substantial professional judgment, and the results might be questioned if developed by a government agency; therefore, the committee recommends that the DVA arrange for a nongovernmental organization with appropriate experience in historical exposure reconstruction to develop and test potential models of herbicide exposure for use in studies of Vietnam veterans.

Recommendation 5. The exposure reconstruction models developed according to Recommendation 4 should be evaluated by an independent, nongovernmental scientific panel established for this purpose.

Herbicide exposure reconstruction models for Vietnam veterans must be thoroughly evaluated before epidemiologic studies based on these models proceed. The committee has identified three possible approaches to such an evaluation, which are discussed in more detail in Chapter 6: (1) internal consistency checks, (2) comparisons of exposure measures based on the reconstruction model with actual serum dioxin measurements, and (3) assessments of the association between exposure reconstruction measures and health outcomes shown in occupational or environmental studies to be associated with herbicides. Scientific judgment is required in interpreting the results of such an evaluation, so the committee cannot specify explicit criteria for acceptance or rejection of the new exposure reconstruction models in advance of their development and testing. Thus, the committee recommends that an independent, nongovernmental scientific panel be established to review the results of the proposed evaluation studies and to judge the validity and feasibility of the exposure reconstruction models. This panel should have expertise in historical exposure reconstruction

and in epidemiology. In order to maintain the public and scientific credibility of the study, the panel members should be nongovernmental and independent of the organization that develops the exposure reconstruction models.

Recommendation 6. If the scientific panel proposed in Recommendation 5 determines that a valid exposure reconstruction model is feasible, the Department of Veterans Affairs and other government agencies should facilitate additional epidemiologic studies of veterans.

A number of possible epidemiologic studies could provide additional information on the health effects of exposure to herbicides in Vietnam beyond what is already known. Highest research priority should be given to those health effects for which additional study is likely to change the balance of the evidence for or against an association. This includes

- a. health outcomes for which current evidence is limited/suggestive of an association (lung and respiratory cancers, multiple myeloma, and prostate cancer);
- b. health outcomes for which current evidence is insufficient or inadequate to determine whether an association exists, but which, in the committee's judgment, are plausible based on animal toxicologic data (such as nasal/nasopharyngeal cancer) or for which there are known associations with related chemical compounds in humans (such as liver cancer and polychlorinated biphenyls; Nicholson, 1987);
- c. health outcomes for which the typical age at onset has not yet been reached by members of the Vietnam veteran cohort (such as prostate cancer).

The committee also recommends that priority be given to additional research on reproductive effects that would help clarify the possible effects of herbicides. In particular, the committee believes that extensive reanalysis of the Ranch Hand reproductive data could shed additional light on these questions (see Chapter 9 and Appendix C).

Although there is sufficient evidence of an association between occupational or environmental exposures to herbicides and non-Hodgkin's lymphoma, Hodgkin's disease, and soft tissue sarcomas, the existing information on dose-response relationships is incomplete, especially with regard to Vietnam veterans. If a valid exposure reconstruction method can be developed, it might be applied to the exposure data available from existing case-control studies to provide additional dose-response evaluations. Additional refinement of the clinical and pathological definitions of soft tissue sarcomas in epidemiologic studies would also help to determine which of the specific cancers in this class are associated with herbicides or TCDD.

The committee recognizes that the recommendations for development of a historical exposure reconstruction model and its use in epidemiologic studies might seem at variance with the Centers for Disease Control (CDC), White House Agent Orange Working Group (AOWG), and Office of Technology Assessment (OTA) conclusions made in 1986 with regard to the congressionally mandated Agent Orange Study. The committee has come to a different conclusion for four reasons: First, the CDC-AOWG-OTA conclusions were based in large part

on serum TCDD measurements, which the committee feels are insufficient for validating exposure to herbicides used in Vietnam, as explained in Chapter 6. Second, the arguments underlying the earlier conclusion that individuals in combat units were widely dispersed and that troop movement data are incomplete imply that exposure measurements may be imprecise, not that they are invalid. However, these arguments do suggest that historical reconstruction of exposure will have nondifferential misclassification errors that will lead to underestimates of the relative risk of health outcomes if an association is in fact present. Third, the committee is proposing the use of more, but less formal, information on exposure than was considered in 1986. This includes the development and use of informal information on perimeter spraying, which might account for more meaningful herbicide exposure than the aerial spraying documented on the HERBS tapes. Finally, the committee does not know whether the approach it proposes will prove valid or whether new methods will identify a sufficient number of highly exposed Vietnam veterans for an epidemiologic study. In the committee's judgment, however, the likelihood that this approach will be successful is sufficient for it to be recommended.

Mandated Research Efforts

For the purposes of further research on the health effects of Vietnam service, Public Law 102-4 mandates that the DVA establish four specific programs that are subject to initiation, continuance, or discontinuation, depending on the findings of this IOM report, and the committee is charged with making recommendations about these specific mandates. The DVA has no specific plans for any of these research efforts beyond the minimal descriptions given in the law, so the committee is able to comment on them in only the broadest terms.

The committee's recommendations speak to its legislative mandate to determine "the feasibility of conducting additional scientific research on" health hazards resulting from exposure to dioxin and herbicides used in Vietnam, the research mandate in section 8 of Public Law 102-4. As previously stated, the committee feels that a series of epidemiologic studies of veterans could yield valuable information if a new, valid exposure reconstruction model can be constructed.

Section 6 of Public Law 102-4 requires the DVA to "compile and analyze, on a continuing basis, all clinical data" that (1) are obtained in connection with DVA examinations and treatment of Vietnam veterans, and (2) are likely to be scientifically useful in determining the association between disabilities experienced by these veterans and exposure to dioxin or herbicides. Such a system, called the Agent Orange Registry (see Chapter 2), currently exists. Section 7 of the law calls for the establishment of a system for the collection and storage of voluntarily contributed samples of blood and tissue of veterans who served in Vietnam. Balancing the strengths and weaknesses of stored biological samples and clinical data for research purposes, the committee feels that systems of this sort have scientific value, but only to the extent that they are components of specific, well-designed studies; see, for instance, National Research Council (1991). In the absence of a clear study design to guide such activities, and without resolution of important design, quality control, and ethical issues

regarding tissue banks, the committee does not recommend the establishment at this time of the clinical data and tissue archiving systems described in sections 6 and 7 of the law.

The final mandate in Public Law 102-4 on which the committee must comment calls for the testing of serum of Vietnam veterans who apply for medical care or file a disability compensation claim for TCDD (section 9). The purpose of this mandate is not stated in the legislation. If research purposes are contemplated, the committee's discussion about tissue archiving systems applies, and such a program would not be recommended at this time. It is also possible that this program is intended to provide information on individual exposure to dioxins or herbicides to aid in individual compensation decisions. The committee cannot make recommendations for DVA policy, but notes that the finding in Chapter 6 that individual TCDD serum levels in Vietnam veterans are usually not meaningful (because of common background exposures to TCDD, poorly understood variations among individuals in TCDD metabolism, relatively large measurement errors, and exposure to herbicides that did not contain TCDD) might apply to this mandate.

REFERENCES

- Alavanja MC, Merkle S, Teske J, Eaton B, Reed B. 1989. Mortality among forest and soil conservationists. *Archives of Environmental Health* 44:94-101.
- Axelsson O, Sundell L. 1974. Herbicide exposure, mortality and tumor incidence. An epidemiological investigation on Swedish railroad workers. *Scandinavian Journal of Work, Environment, and Health* 11:21-28.
- Blair A, Grauman DJ, Lubin JH, Fraumeni JF Jr. 1983. Lung cancer and other causes of death among licensed pesticide applicators. *Journal of the National Cancer Institute* 71:31-37.
- Boffetta P, Stellman SD, Garfinkel L. 1989. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. *International Journal of Cancer* 43:554-559.
- Burmeister LF, Everett GD, Van Lier SF, Isacson P. 1983. Selected cancer mortality and farm practices in Iowa. *American Journal of Epidemiology* 118:72-77.
- Cantor KP, Blair A. 1984. Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. *Journal of the National Cancer Institute* 72:251-255.
- Eriksson M, Hardell L, Berg NO, Moller T, Axelsson O. 1981. Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. *British Journal of Industrial Medicine* 38:27-33.
- Eriksson M, Hardell L, Adami HO. 1990. Exposure to dioxins as a risk factor for soft tissue sarcoma: a population-based case-control study. *Journal of the National Cancer Institute* 82:486-490.
- Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K, Suruda AJ. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *New England Journal of Medicine* 324:212-218.

- Green LM. 1991. A cohort mortality study of forestry workers exposed to phenoxy acid herbicides. *British Journal of Industrial Medicine* 48:234-238.
- Hardell L. 1981. Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. *Scandinavian Journal of Work, Environment, and Health* 7:119-130.
- Hardell L, Bengtsson NO. 1983. Epidemiological study of socioeconomic factors and clinical findings in Hodgkin's disease, and reanalysis of previous data regarding chemical exposure. *British Journal of Cancer* 48:217-225.
- Hardell L, Eriksson M. 1988. The association between soft tissue sarcomas and exposure to phenoxyacetic acids: a new case-referent study. *Cancer* 62:652-656.
- Hardell L, Sandstrom A. 1979. Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *British Journal of Cancer* 39:711-717.
- Hardell L, Eriksson M, Lenner P, Lundgren E. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *British Journal of Cancer* 43:169-176.
- Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF. 1986. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *Journal of the American Medical Association* 256:1141-1147.
- Karnow S. 1991. *Vietnam: A History*. New York: Penguin.
- Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. 1991. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 338:959-964.
- Morrison H, Savitz D, Semenciw R, Hulka B, Mao Y, Morison D, Wigle D. 1993. Farming and prostate cancer mortality. *American Journal of Epidemiology* 137:270-280.
- National Research Council, Committee on National Monitoring of Human Tissues, Board on Environmental Studies and Toxicology, Commission on Life Sciences. 1991. *Monitoring Human Tissues for Toxic Substances*. Washington, DC: National Academy of Sciences.
- Nicholson WJ. 1987. Report to the Workers' Compensation Board on Occupational Exposure to PCBs and Various Cancers. Industrial Disease Standards Panel Report No. 2. Toronto: Ontario Ministry of Labour.
- Persson B, Dahlander A-M, Fredriksson M, Brage HN, Ohlson C-G, Axelson O. 1989. Malignant lymphomas and occupational exposures. *British Journal of Industrial Medicine* 46:516-520.
- Riihimäki V, Asp S, Hernberg S. 1982. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland: first report of an ongoing prospective cohort study. *Scandinavian Journal of Work, Environment, and Health* 8:37-42.
- Riihimäki V, Asp S, Pukkala E, Hernberg S. 1983. Mortality and cancer morbidity among chlorinated phenoxyacid applicators in Finland. *Chemosphere* 12:779-784.
- Saracci R, Kogevinas M, Bertazzi PA, Bueno De Mesquita BH, Coggon D, Green LM, Kauppinen T, L'Abbe KA, Littorin M, Lynge E, Mathews JD, Neuberger M, Osman J, Pearce N, Winkelmann R. 1991. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 338:1027-1032.

- Swaen GMH, van Vliet C, Slangen JJM, Sturmans F. 1992. Cancer mortality among licensed herbicide applicators. *Scandinavian Journal of Work, Environment, and Health* 18:201-204.
- Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. 1987. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxy herbicide and chlorinated phenol exposure in western Washington. *Journal of the National Cancer Institute* 78:899-910.
- Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. 1990. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1:349-356.
- Zober A, Messerer P, Huber P. 1990. Thirty-four-year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. *International Archives of Occupational and Environmental Health* 62:139-157.